

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-629

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-629

Aventis Pharmaceutical Inc.
Attention: Steve Caffé, M.D.
Head, U.S. Regulatory Affairs
200 Crossing Boulevard
P.O.Box 6890
• Bridgewater, NJ 08807-0890

Dear Dr. Caffé:

Please refer to your new drug application (NDA) dated June 18, 2003, received June 18, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Apidra™ (insulin glulisine [rDNA origin]) injection.

We acknowledge receipt of your submissions dated July 18, August 8, September 10, October 24, November 4, 11, 14, 20, and 24, and December 12, 2003; January 14, February 5, 6 (2), 10, 12, 17, and 20, March 17, 25, and 26, and April 6 and 15, 2004.

This new drug application provides for the use of Apidra™ (insulin glulisine [rDNA origin]) injection for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the editorial revision listed below:

The vertical black bar on the carton and vial label must be deleted.

The final printed labeling (FPL) must be identical to, except for including the revision listed, the enclosed labeling (text for the package insert, text for the patient package insert, immediate container and carton labels submitted on April 15, 2004). These revisions are terms of the NDA approval. Marketing the product before making the revision, exactly as stated, in the product's labeling may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-629.**" Approval of this submission by FDA is not required before the labeling is used.

We acknowledge your plan to submit a prior approval supplement to incorporate a unique insulin color code for your product as stated in your April 15, 2004, submission.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-629.**" Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages new born up to four years and deferring pediatric studies for ages five to seventeen years for this application.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

- Deferred pediatric study under PREA for the treatment of diabetes mellitus in pediatric patients ages five to seventeen years old.

Final Report Submission: December 21, 2007

Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "**Required Pediatric Study Commitment**".

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

We also remind you of your agreement in the submission dated the March 25, 2004, to perform a study of the antimicrobial effectiveness of m-cresol at the lowest concentration observed at the needle end of the catheter tubing during the pump studies and to submit the data within one year after the approval of the NDA.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Julie Rhee, Regulatory Project Manager, at (301) 827-6424.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.

Director

Office of Drug Evaluation II

Center for Drug Evaluation and Research

- Enclosures:
1. Package insert submitted April 15, 2004
 1. Patient package insert submitted April 15, 2004
 2. Immediate container label submitted April 15, 2004
 3. Carton label submitted April 15, 2004